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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,811	05/14/2001	Robert E. Reiter	02307K-141581	9472

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EXAMINER	
HELMS, LARRY RONALD	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/854,811	REITER ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53,58-72,74 and 77-97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53,58-72,74 and 77-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

1. The request filed on 4/16/04 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/854,811 is acceptable and a RCE has been established. Claims 53, 58-74, 77-97 are pending and are currently under prosecution. An action on the RCE follows.

2. Claims 53, 78 have been amended.

3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

4. The following Office Action contains NEW GROUNDS of rejection.

Rejections Withdrawn

5. The rejection of claims 53, 74, and claims 77-81, 97 under 35 U.S.C. 103(a) as being unpatentable over Au-Young (U.S. Patent 5,856,136, filed 7/96) and further in view of Spitler (U.S. Patent 5,738,867, filed 6/95) is withdrawn in view of the amendments to the claims.

6. The rejection of claims 78-97 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

7. The rejection of claims 53, 58-73, and newly added claims 77-97 under 35 U.S.C. 112, first paragraph is withdrawn in view of the NEW GROUND of rejection.

The following is a NEW GROUND of rejection

8. Claim53, 58-72, 74, 77-97 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of inducing an anti-tumor immune response to PSCA in any cancer subject that expresses PSCA or cells that express PSCA wherein the method comprises administration of SEQ ID NO:2 or any immunogenic portion of SEQ ID NO:2 or specific regions of SEQ ID NO:2 wherein the subject is human. The claims encompass administration of SEQ ID NO:2 or any

immunogenic fragment of SEQ ID NO:2 to a human for inducing an anti-tumor response.

The specification teaches the human PSCA protein of SEQ ID NO:2. The specification discloses PSCA protein or fragments for use as a tumor antigen in a vaccine for generating a humoral and cell-mediated immunity for anti-cancer therapy (see page 60). In addition, the claims encompass administration of SEQ ID NO:2 or specific fragments of SEQ ID NO:2 wherein the specification does not teach that just any immunogenic fragment of SEQ ID NO:2 can be used in humans to induce an anti-tumor response.

Since the therapeutic indices of immunotherapeutic regimens can be species- and model-dependent, it is not clear that reliance on the generation of disclosing certain antigen specificities of antigens on certain tumor cell lines or tumor cells accurately reflects the relative ability of the claimed methods to make such compositions to treat tumorous disease, encompassed by the claims.

There is insufficient guidance and direction to prepare tumor adjuvant vaccines using any PSCA-antigen-derived peptide. The claims encompass administering SEQ ID NO:2 or fragments of SEQ ID NO:2 and it is well known that not every fragment of a protein can be used to produce antibodies or whether the fragments or the entire protein can produce an anti-tumor response that is encompassed in the claims. While an antibody can be made to the protein or any fragment of a protein not every protein or fragment would produce an immune response that would result in an anti-tumor response. Due to the location of the fragment in the properly folded protein only those

that would be recognized on the surface of the protein could possibly be used for anti-tumor responses.

The specification provides insufficient guidance and objective evidence that SEQ ID NO:2 or immunogenic fragments of SEQ ID NO:2 in pharmaceutical compositions and or vaccines formulations would predictably invoke an anticancer or immuntherapeutic response. The specification provides no guidance on the administration of the claimed protein or fragments in vivo or in vitro.

In general, the treatment of cancer is at most unpredictable as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. Further, Bellone *et al.* . (Immunology Today, v20 (10), 1999, pp.457-462) summarize the current state of the art of peptide immunotherapy including clinical trials where "there is usually a poor correlation between induction of specific T-cells and the clinical responses" (page 457, 2nd column). Bellone *et al.* teach the disadvantages of peptide cancer immunotherapy in that (1) there is no direct evidence for a role in tumor rejection, (2) the therapy is applicable to few patients, (3) risk of generating tumor escape mutants, and (4) risk of

autoimmune reactions (page 461, Box 1). Indeed, Gaiger *et al.* (Blood, Volume 96, No. 4, August 2000, pages 1480-1489) chose to evaluate the Wilm's tumor antigen (WT1) as a potential immunotherapeutic as it is well known in the art that WT1 protein expression is more abundant in leukemia cells than in normal hematopoietic ells. However, WT1 peptide immunization did not show any effect on tumor growth in-vivo (Figure 10, page 1486). In addition just because the protein or peptide is "immunogenic" does not mean it is going to be effective as a antitumor response generator. As stated in Gaiger et al (cited above) the peptide must bind MHC-1 and induce a CTL response (see abstract). In addition, Bellone et al (cited above) states that the peptide should facilitate an effective recruitment of tumor specific CTLs (see page 457). Thus, not just any "immunogenic fragment" will induce the CTLs and be useful as a anti-cancer vaccine as encompassed by the claims. This is underscored by Lu et al (Cancer res 2002 62:5807-12) which teaches computer algorithms predicted five peptides from PSMA that were predicted to induce antigen-specific CTLs, however, only one peptide induced the CTLs that were effective at recognizing prostate tumor cells expressing PSCA (see abstract) and each peptide needed to be tested to determine if it would produce a CTL response (see page 5811). Thus, without actually testing the peptides it would be unpredictable whether any of the claimed peptides or protein would function in an anti-tumor cancer vaccine directed against any of the cancers claimed or produce the required CTL response.

All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable for of skill in the art to use the protein of SEQ ID NO:2 or immunogenic fragments thereof in pharmaceutical compositions or vaccine formulations as contemplated in the disclosure. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

The response filed 4/16/04 has been carefully considured but is deemed not to be persuasive. The response states that applicant's have amended the claims to recite "immunogenic fragments" of SEQ ID NO:2 and have added specific cancers and the specification provided assays for identifying immunogenic peptides as well as administration of the peptides to raise an immune response as in Example 18 (see pages 1-2 of response).

In response to this argument, the claims are clearly drawn to producing an anti-cancer immune response in a human, i.e. a cancer vaccine. The amendments to the claims to add "immunogenic fragments" does not overcome the enablement because while one may determine what an "immunogenic fragment" of SEQ ID NO:2, it is known that almost any fragment of any peptide may be "immunogenic" in the right context of producing an "immune response". While one may identify such peptides or proteins, as the art cited above states that cancer vaccines, which is encompassed by the claims is

unpredictable. In addition just because the protein or peptide is "immunogenic" does not mean it is going to be used as a antitumor response generation. As stated in Gaiger et al (cited above) the peptide must bind MHC-1 and induce a CTL response (see abstract). In addition, Bellone et al (cited above) states that the peptide should facilitate an effective recruitment of tumor specific CTLs (see page 457). Thus, not just any "immunogenic fragment" will induce the CTLs and be useful as a anti-cancer vaccine as encompassed by the claims. Thus, it would be unpredictable whether SEQ ID NO:2 or any "immunogenic fragments" of SEQ ID NO:2 would produce an anti-tumor immune response in the human patient. Example 18 is only an example of producing antibodies in a mouse which is typical in the art of monoclonal antibody production. The mouse did not have cancer that expressed PSCA or any of the cancers in the claims.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ~~Yvonne Eyle~~ CHRISTINA CHAN, can be reached on (571) 272-0871.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832